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CASE REPORT

# High-Dose Verapamil in Episodic and Chronic Cluster Headaches and Cardiac Adverse Events: Is It as Safe as We Think?

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**Abstract** Cluster headache (CH) is a primary headache disorder with relatively effective treatments. Although few sufficiently controlled trials are available, verapamil is recommended as the first-line prophylactic drug for CH by the French Headache Society (with a low level of evidence, level B) and by the EFNS (European Federation of Neurological Societies, level A). Daily doses of more than 480 mg (and up to 1200 mg daily) are frequently used off-label, while 360 mg daily is the only dosage to have demonstrated its effectiveness in a double-blind trial against placebo, and the usual label posology used by cardiologists is 240 mg daily in hypertension. We report the case of a 19-year-old man who was self-reported to our cardiology consultation for dyspnea and asthenia for 18 months. His medical history consisted of CH crisis for 4 years treated by verapamil 720 mg/day for 18 months with relatively good efficiency. His electrocardiogram (ECG) showed a sinus bradycardia at 40 bpm with a first-degree atrio-ventricular block. Evolution was favorable after progressive verapamil discontinuation. Analysis performed on the French Pharmacovigilance Database between July 1, 2000 and December 1, 2014 found four other cases of cardiac adverse events related to high-dose verapamil used in CH prevention (two cases of syncope with complete atrio-ventricular block with verapamil 1200 and 240 mg daily, respectively, one syncope related to sick sinus syndrome with verapamil 360 mg daily, and one case of sinus bradycardia with verapamil 720 mg daily). Although available studies seem to demonstrate an apparent good tolerance, this off-label practice should not be considered as standard of care and requires strict cardiac monitoring, as suggested by the Agence Nationale de Sécurité du Médicament (ANSM) in a recent re-evaluation of the benefit/risk ratio of high-dose verapamil used in CH prevention.

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## Key Points

Despite a low level of recommendation, verapamil is considered as the first-line prophylactic drug for cluster headaches.

High-dose verapamil seems to be efficient in pain management in selected and appropriate patients.

Serious cardiac adverse events could occur with high-dose verapamil and patients therefore require strict electrocardiogram monitoring.

## Introduction

Cluster headache (CH) is a primary headache disorder which is classified with similar conditions known as the trigeminal autonomic cephalalgias in the International Headache Society diagnostic criteria [1]. It is a rare but very disabling condition. The disease has typical and therefore easily recognizable clinical features and specific criteria have been proposed. At least five attacks fulfilling the following criteria are required for diagnosis: severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 min if untreated; headache accompanied by at least one of the following: ipsilateral conjunctival injection and/or lacrimation, ipsilateral nasal congestion and/or rhinorrhea, ipsilateral eyelid edema, ipsilateral forehead and facial sweating, ipsilateral miosis and/or ptosis; sense of restlessness or agitation; frequency of the attacks from once a day to eight per day; and headaches not attributed to another disorder [1]. The intensity of the attacks and the consequent disability are such that patients require rapid diagnosis and appropriate treatment. Effective options for both abortive and preventive treatment are currently available. These options are supported by updated international therapeutic guidelines [2].

Based on two old clinical trials [3, 4], verapamil is recommended off-label [5] as the first-line prophylactic drug for CH [2, 6]. The usual label posology recommended is 240 mg daily (with a maximum of 360 mg daily) in hypertension [5]. High-dose verapamil (480–600 mg daily) may be used in cardiology practice in the rare short-coupled variant of torsade de pointes syndrome, but it is usually given with the safety measure of an implantable cardioverter defibrillator to prevent extreme bradycardia [7]. In CH prevention, daily verapamil doses of more than 480 mg (and up to 1200 mg daily) are frequently used [8, 9]. This cure seems to involve 14.8 % of CH patients [10] and is considered by neurologists as well tolerated and safe, although verapamil 360 mg daily is the only dosage to have demonstrated its effectiveness in a double-blind trial against placebo [4].

CH pathophysiology and the mechanisms underlying the effectiveness of verapamil in pain management are not yet completely understood. One explanation for the use of a higher verapamil dose in CH than in hypertension is that at cardiologic doses, verapamil acts only as a calcium channel blocker [11]. At a higher dose, verapamil could also modulate central neuronal activity and affect hypothalamic and noradrenergic functions and the opiate system, which is particularly sensitive to high-dose verapamil [12–16].

The aim of the present study was to discuss this off-label use of high-dose verapamil in CH prevention, its security, and the precautions inherent to this practice.

## Case Report

We report the case of a 19-year-old man who was self-reported to our cardiology consultation for dyspnea and asthenia for 18 months. He was on work disability for 12 months because of a complete failure to realize any effort. His medical history only consisted of very debilitating CHs for 4 years, which were treated with verapamil 720 mg/day for 18 months with good efficiency. He did not have any past cardiologic history. There was no renal function assay available. His other medications included sumatriptan 6 mg and ketoprofene 100 mg (extended-release formulation). No electrocardiogram (ECG), either at baseline condition or during clinical follow-up, was available. His examination highlighted a cardiac frequency at 40 bpm without any signs of heart failure. His ECG showed a sinus bradycardia at 40 bpm with a first-degree atrio-ventricular block (Fig. 1). There was no heart rate increase despite the achievement of lower limb exercise for several minutes, indicating a severe chronotropic incompetence that could explain the symptoms described by the patient. Unfortunately, no verapamil blood measurement was taken, but we can expect that it would have been above the recommended therapeutic concentrations [17]. Verapamil was gradually stopped. The patient was summoned 1 week later to undergo a new ECG. The latter showed the recovery of a 70/min sinus rhythm without any atrio-ventricular block and the complete disappearance of dyspnea and asthenia. The patient was able to return to work 3 weeks after verapamil discontinuation. Regarding his CHs, the verapamil was replaced by levetiracetam 1000 mg daily associated with sumatriptan 6 mg and ketoprofene 100 mg (extended-release formulation), with a favorable evolution. This case was notified to the Centre Régional de Pharmacovigilance de Basse Normandie and then registered in the French Pharmacovigilance Database. The intrinsic causality assessment retained for verapamil in our case was ‘very likely’ (C3S3 or I6) and the extrinsic causality assessment (bibliographic causality assessment) retained was ‘expected effect’ (B4) according to the French method for causality assessment [3].

## Review of the French Pharmacovigilance Database

Analysis performed on the French Pharmacovigilance Database between July 1, 2000 and December 1, 2014 found four other cases of cardiac adverse events related to

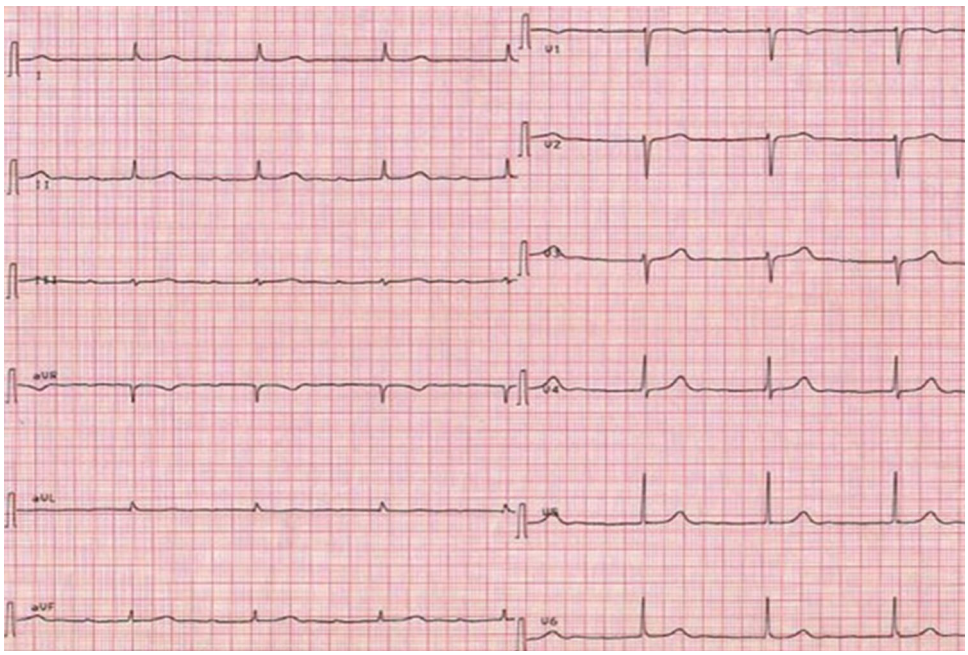

**Fig. 1** Electrocardiogram made during the patient examination showing a sinus bradycardia at 40 bpm with a first-degree atrio-ventricular block

the use of high-dose verapamil in CH prevention. The assessment of causality was performed according to the French method for causality assessment [18]. Terms used for this analysis included verapamil, cephalalgia, atrio-ventricular block, bradycardia, syncope, cardiac disorders and cardiac arrests. For the verapamil causality assessment, only the cases with a 'probable' imputability were maintained. Two of them were cases of syncope with complete atrio-ventricular block (verapamil 1200 mg daily in a 54-year-old man and 240 mg daily in a 53-year-old man, respectively), one was a syncope related to sick sinus syndrome (verapamil 360 mg daily associated with a lithium intoxication in a 42-year-old man) and the last was a case of sinus bradycardia (verapamil 720 mg daily in a 24-year-old man). None of these patients had a past cardiologic history. There was no renal function assay available for these patients in either baseline condition (before introducing verapamil) or during the cardiac adverse event. Moreover, there was no blood verapamil measurement performed for these patients.

## Discussion

Although few sufficiently controlled trials are available [3, 4], verapamil is recommended off-label [5] as the first-line prophylactic drug for CH by the French Headache Society (with a low level of evidence, level B) [6] and by the EFNS (European Federation of Neurological Societies, level A) [2]. Frequently and without any double-blind trial against placebo (the only dosage which has demonstrated its effectiveness in a double-blind trial against placebo is 360 mg daily [4]), daily doses of verapamil >480 mg (and up to 1200 mg daily) [8, 9] are used off-label and are considered well tolerated and safe [4], while the usual label posology recommended is 240 mg daily (with a maximum of 360 mg daily) in hypertension [5]. Bussone et al. [3] published in 1990 a study comparing verapamil 360 mg daily for 8 weeks with lithium 900 mg daily in an American Academy of Neurology (AAN) Class II study. Thirty patients with chronic CH participated in this crossover study, and outcomes included the intensity, frequency, and duration of attacks during the trial period. A total of 50 % of patients in the verapamil group and 37 % of those in the lithium group experienced an improvement in the headache index, compared with the run-in period ($p < 0.01$). Leone et al. [4] studied verapamil at 360 mg daily versus placebo for 2 weeks in 30 patients in an AAN Class III study. The primary endpoint was the reduction in the frequency of the attacks per week. Verapamil was found to be superior to placebo. Patients taking verapamil experienced 0.6 attacks per day, compared with 1.65 per day in the placebo group ($p < 0.001$). Only non-serious adverse effects were reported. Regarding these two studies, verapamil seems to be a very effective treatment for pain management in CH.

Mechanisms of action of verapamil in CH are not completely known. Neither is the pathogenesis of CH understood. Initially, the hypothesis of a vascular genesis was raised and therefore verapamil seemed to be interesting in this context [19]. Now this hypothesis seems outdated and the exact mode of action of verapamil in relief of pain management in CH is not clear. Verapamil is a phenylalkylamine derivative which exerts its calcium antagonist effect by interfering with the slow calcium

channels and thus modulates the calcium flux across cell membranes [11]. Other observations indicated that calcium antagonists act via a mechanism which is not only vascular. Variations in regional cerebral blood flow and cerebrovascular response to various stimuli were monitored in groups of CH and migraine patients while undergoing treatment with calcium antagonists [20, 21]. Results showed that verapamil was more efficacious than other calcium antagonists in treating CH, but induced minimal changes in cerebral circulation which, in any event, were less than those produced by other calcium antagonist drugs. This poor correlation between vascular effects and clinical efficacy suggests that the cerebral vascular bed may not be the main site of action of verapamil in CH prophylaxis. Other studies indicated that verapamil is able to modulate central neuronal activity by several mechanisms: it may influence muscarinic [12], serotoninergic [13], dopaminergic, and noradrenergic receptors [14], it may also affect hypothalamic and noradrenergic functions [15]. Of all the cerebral transmitter systems, it is the opiate system which is particularly sensitive to verapamil. When the drug is administered in high doses, it is able to modify the analgesic effect of morphine. It could also modulate the inhibitory action that hypothalamic peptides exert on morphine-induced analgesia and appears able to restore correct function of the analgesic system in the presence of an excess of these hypothalamic peptides—an action the drug exerts after a short latency period [16].

However, despite the undeniable effectiveness of verapamil in CH prevention, cardiac adverse events should not be overlooked. In a recent study, Lanteri-Minet et al. (Table 1) reviewed 29 patients with CH who were taking 720 mg or more of verapamil daily [10]. Eleven patients (38 %) were found to have ECG abnormalities with bradycardia ($n = 7$), first-degree atrio-ventricular block ($n = 2$), second-degree atrio-ventricular block ($n = 1$) and third-degree atrio-ventricular block ($n = 1$) [10]. ECG changes have been considered a cardiac serious adverse event in four patients (14 %). Authors did not find any significant predictive factor except verapamil dose. Indeed, cardiac serious adverse events concerned patients using an average very high verapamil daily dose of 990 ± 315 mg. Cardiac serious adverse event onset could be delayed (three patients presented cardiac serious adverse events at 72, 71, and 24 months after the very high dose was achieved). Cohen et al. [22] audited the ECG abnormalities in 217 patients with CH on verapamil therapy at a mean dose of 512 mg daily (Table 1). Among the 217 patients, ECG was only available in 128 patients (59 %). Thirteen patients presented first-degree atrio-ventricular block, four patients had junctional rhythm, and one had second-degree atrio-ventricular block. Bradycardia <60 bpm was noticed in 39 patients. In eight patients, the PR interval was lengthened, but not to >0.2 s. Authors concluded that high-dose verapamil was linked to frequent severe cardiac outcomes (estimated to one in five) and that a substantial number of patients did not have ECG monitoring as recommended. This ECG monitoring seems to be particularly important in that significant ECG abnormalities can develop with time, even on a stable dose. Following publications regarding ECG abnormalities, the recommendations for titration of verapamil have evolved. A starting dose of verapamil 80 mg three times a day, increasing by 80 mg each week until a dose of 480 mg daily is reached has recently been proposed. Beyond 480 mg, an increase in the daily dose of 80 mg every 15 days is recommended in order to have a consistent decline on increasing doses [23]. Other teams offer faster titration in patients with more than two seizures a day, starting at 120 mg twice daily and increasing the daily dose by 120 mg every 48 h [24].

All these results show that high-dose verapamil used in CH may not be as well tolerated as suggested and serious cardiac adverse events could occur in practice. Considering the frequent use of high daily doses, cardiac safety assessment with systematic ECG monitoring is essential in the management of CH patients treated with verapamil, particularly in elderly patients who are at higher risk of cardiac conduction disorders [25]. In daily practice, this

**Table 1** Adverse cardiac events with high-dose verapamil use

| | Lanteri-Minet et al. [10] | Cohen et al. [22] |
|---|---|---|
| Number of patients | 29 | 217 |
| Average verapamil dosage, mg/day | 877 | 512 |
| Number of ECG available (%) | 29 (100 %) | 128 (59 %) |
| Number of ECG abnormalities (%) | 15 (52 %) | 57 (44 %) |
| Type of abnormalities (%) | Bradycardia: 7 (24 %) | Bradycardia: 39 (30 %) |
| | First-degree AV block: 2 (7 %) | First-degree AV block: 13 (10 %) |
| | Second-degree AV block: 1 (3 %) | Second-degree AV block: 1 (1 %) |
| | Third-degree AV block: 1 (3 %) | Third-degree AV block: 0 (0 %) |
| | Junctional rhythm: 4 (14 %) | Junctional rhythm: 4 (3 %) |

*AV* atrio-ventricular, *ECG* electrocardiogram

recommendation seems not to be systematically applied [22]. Our work highlights the need for a systematic ECG before verapamil initiation in order to screen absolute (such as high-grade atrio-ventricular block or sick sinus syndrome in patients without a permanent pacemaker) and relative (such as first-degree atrio-ventricular block) verapamil contraindications and an annual ECG follow-up along with a cardiologist visit because of the risk of delayed cardiac serious adverse events. It could also seem reasonable to perform at least one trans-thoracic echocardiography before verapamil initiation (particularly for high doses) in order to assess the left ventricular ejection fraction. In the setting of 'cardiologic' verapamil use, the European Society of Cardiology guidelines [26] recommend an echography before verapamil initiation. In fact, verapamil is a potent negative inotropic agent that could induce cardiogenic shock in case of systolic heart failure [26] or in case of voluntary poisoning [27]. These recommendations seem all the more important to observe if the patient is old or has significant cardiovascular comorbidities. Indeed, given literature data [10, 25] and the French Pharmacovigilance Database, patients presenting with serious cardiac adverse events seem to be the oldest.

Verapamil is metabolized by cytochrome P450 (CYP) 3A4 to inactive and to active metabolites [28], the most important being norverapamil, which is less cardiotoxic than its parent compound [29]. Therefore, CYP 3A4 inducers and inhibitors are likely to result in decreased and increased plasma levels of verapamil, respectively [30–32]. Co-medication with other drugs indicated in CH such as triptans, prednisolone or ergotamine, which are also metabolized by CYP 3A4, could induce a drug–drug interaction with verapamil [33, 34]. Verapamil is also a probe inhibitor of transporter P-glycoprotein (P-gp). P-gp is located throughout the body, including the gastrointestinal tract, where it can directly limit oral drug absorption [35]. Previous studies have demonstrated that short-term usual-dose verapamil inhibits intestinal P-gp, whereas long-term usual-dose administration may induce P-gp expression [36]. Co-medication with prednisolone, which is also transported by P-gp, may therefore induce a drug–drug interaction with verapamil [37]. It is important to note that high-dose verapamil impact on P-gp and CYP 3A4 expression has never been studied but we can suppose a major impact on co-medication oral bioavailability. Note that an ECG will be required in case of even temporary co-medication with CYP 3A4 or P-gp inducers/inhibitors. Another important co-medication is the lithium coprescription. Indeed, lithium is an available CH treatment supported by international therapeutic guidelines [2], but lithium is also a well known medication which may induce bradycardia, sick-sinus syndrome and atrio-ventricular block, especially in cases of intoxication [38]. Finally, off-label use of a drug is still a high-risk practice. However, in this case, the use of high-dose verapamil is an especially high-risk practice as it exposes patients to serious cardiac side effects (ECG abnormalities) and to the risk of major drug–drug interactions.

Finally, it is unfortunate that no blood drug confirmatory assay was achieved in clinical studies and in cases reported in the French Pharmacovigilance Database. Therapeutic plasma levels of verapamil are 0.20–0.35 μg/mL, with toxic concentration at values exceeding 9 μg/mL [17]. A confirmatory assay would allow the link between high-dose verapamil and serious cardiac adverse events occurrence to be tested, it could help clinicians to avoid 'toxic' doses and it could also inform the verapamil dosage escalation without reaching the toxicity threshold.

Our recommendations are consistent with those published recently by the Agence Nationale de Sécurité du Médicament (ANSM), which recently re-evaluated the benefit/risk ratio of high posology verapamil used in CH prevention [39]. This commission gave a favorable opinion to set up a temporary recommended use for verapamil administered orally in CH prophylactic treatment depending on strict adherence to the procedures for monitoring listed in the temporary recommended use protocol. The commission also recommends that an ECG be performed and a cardiologist's opinion sought before verapamil initiation and new ECGs performed when adding or stopping any medication which could affect verapamil plasma concentrations as part of a drug–drug interaction. The French Headache Society guidelines [6] also recently published official guidelines regarding the verapamil titration protocol and the absolute necessity of strict ECG monitoring. The French Headache Society guidelines seem also more reluctant than the EFNS guidelines regarding the level of recommendation of verapamil used in CH [2, 6].

## Study Limitations

Although this study highlights interesting elements, it remains a case study with all the limitations that entails. Moreover, the French Pharmacovigilance Database probably underestimates the real number of serious cardiac adverse events due to high-dose verapamil and it is therefore difficult to know the real incidence of these side effects in real life.

## Conclusions

Safety issues remain rightfully prominent with high-dose verapamil in CH [22]. Serious cardiac adverse events, although a very infrequent direct event from high-dose verapamil, nevertheless remain a risk as significant ECG

abnormalities can develop with time even on a stable dose [22]. However, the benefits of using verapamil in CH (if necessary at doses exceeding those used by cardiologists in hypertension) for pain management and prevention in selected and appropriate patients seem to be favorable [3, 4]. The above-described case report and the French Pharmacovigilance Database review show that care must be taken when administering off-label high-dose verapamil in CH. This work is consistent with a recent report published by ANSM [39] and the French Headache Society guidelines [6] granting a temporary recommended use for verapamil administered orally in the prophylactic treatment of CH. These recommendations were determined with strict respect of the procedures for monitoring listed in the temporary recommended use protocol, including strict cardiac monitoring. Indeed, serious cardiac adverse events may occur, particularly in elderly patients. Caution must be paid to patient selection and we recommend a cardiologist visit with ECG and echocardiography before any treatment initiation, and strict and regular ECG monitoring all throughout the treatment. Attention must be paid to the patient's co-medication when using verapamil because of the risk of drug–drug interaction and, even more so, because high doses have never been studied in this context. Finally, although high-dose verapamil use in CH prevention is recommended with caution by some clinical studies and expert opinion, this practice remains to date off-label. It seems essential to respect the cardiac monitoring recommendations.

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**Compliance with Ethical Standards**

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**Consent** Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.



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